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ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/996,484	CHOO ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1,2,4,5,7,8,10,11,13-15,21-26,31,34,35,38-47 and 50-54* is/are pending in the application.

5a) Of the above claim(s) *1,2,4,5,7,8,10,11,13-15,21-26,31,35 and 38-47* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *34 and 50-54* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☒ The drawing(s) filed on *28 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/15/2011 has been entered.

Receipt is acknowledged of an amendment, filed 6/15/2011, in which claims 34 and 52-54 were amended. Claims 1, 2, 4, 5, 7, 8, 10, 11, 13-15, 21-26, 31, 34, 35, 38-47 and 50-54 are pending.

Election/Restrictions

Applicant elected Group III without traverse in the reply filed 4/16/2004.

Claims 1, 2, 4, 5, 7, 8, 10, 11, 13-15, 21-26, 31, 35 and 38-47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/16/2004.

Claims 34 and 50-54 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34 and 50-54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new rejection, necessitated by the amendment to the claims in the reply filed 6/15/2011.

Claim 34 recites the limitation "the zinc finger binding domain" in line 4. There is insufficient antecedent basis for this limitation in the claim.

Claim 50 depends from claim 34 and is rejected for the same reason applied to claim 34. Furthermore, claim 50 recites the limitation “the polypeptide” in line 2. There is insufficient antecedent basis for this limitation in the claim. Claim 34 requires the ligand to be bound to “the zinc finger protein,” and claim 50 requires the ligand to be bound to “the polypeptide.” It is unclear if “the polypeptide” of claim 50 is “the zinc finger protein" of claim 34 or if it is a different polypeptide.

Claim 51 depends from claim 34 and is rejected for the same reason applied to claim 34. Furthermore, claim 50 recites the limitation “the polypeptide” in line 2. There is insufficient antecedent basis for this limitation in the claim. Claim 34 requires the ligand to be bound to “the zinc finger protein,” and claim 51 requires the ligand to be bound to “the polypeptide.” It is unclear if “the polypeptide” of claim 51 is “the zinc finger protein" of claim 34 or if it is a different polypeptide.

Claim 52 recites the limitation "the zinc finger binding domain" in lines 5-6. There is insufficient antecedent basis for this limitation in the claim.

Claims 53 and 54 depend from claim 52 and are rejected for the same reason applied to claim 52.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34 and 50-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new rejection.

The claims are drawn to a set of complexes and compositions comprising a zinc finger protein and a ligand. The claims require the ligand to bind to the zinc finger protein, where binding of the ligand modulates the binding of the zinc finger binding domain to a DNA target site. The claims do not limit binding of the ligand to any specific portion of the zinc finger protein. Thus, the ligand may bind to a ligand-binding domain within the zinc finger protein or may bind directly to a Cys2-His2 zinc finger. The rejected claims thus comprise a set of ligands that encompass the ability to bind directly to Cys2-His2 zinc fingers.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification envisions ligands that are molecules of any structure capable of binding to a polypeptide (e.g., page 49, lines 16-18). The specification asserts that

protein binding ligands are well known in the art and include immunoglobulins, antibodies, ATP, cAMP, GABA, Fas ligand, chemical induces of dimerization (CIDs), FK506, FK1012, peptide hormone molecules, retinoic acid, acridine derivatives and other anticancer drugs, etc. (e.g., page 49, lines 18-23). Neither the specification nor art of record teaches that these ligands bind to Cys2-His2 zinc fingers. The specification indicates that it is preferred that ligand of the invention bind polypeptides in a sequence and/or topology dependent manner so that binding can be restricted to a particular target, thus enhancing the specificity of the protein switch, be non-toxic to plants and/or animal cells, and be capable of being taken up by the cells of plants and/or animals (e.g., page 50, line 22 to page 51, line 21). The working examples of the specification describe phage display screening assays used to identify zinc finger domains that bind to a specific DNA target site in the presence of distamycin A, actinomycin D, and echinomycin (Examples 1.1-1.3) and to identify zinc finger binding domains that dissociate from a specific DNA target site in the presence of distamycin A or actinomycin D (Example 1.4). The working examples demonstrate that when distamycin A, actinomycin D, and echinomycin are added to a binding reaction containing the phage selected to bind a particular DNA binding site and the DNA binding site, higher affinity binding between the zinc fingers and the DNA is observed (e.g., Example 1-2). Using the phage of Example 1.1, the specification also demonstrates higher affinity binding of the zinc fingers to the target DNA site in a plasmid contained within cultured cells (e.g., Example 4). Prophetic examples of ligand screening are also provided in the specification (e.g., Examples 6, 12 and 13).

No evidence is presented that supports the assertion that the tested ligands (distamycin A, actinomycin D, and echinomycin) bind Cys2-His2 zinc fingers. The prior art teaches that

distamycin, actinomycin D and echinomycin bind to DNA (Dervan, PBD. Science, Vol. 232, pages 464-471, April 1986; e.g., paragraph bridging pages 464-465; Takusagawa et al. Nature, Vol. 296, pages 466-469, April 1982; e.g., Abstract and Figs. 1-2; Ughetto et al. Nucleic Acids Research, Vol. 13, No. 7, pages 2305-2323, April 1985; e.g., paragraph bridging pages 2305-2306 and Fig. 5). Dervan teaches that distamycin binds AT-rich sequences, and distamycin analogs preferably bind homopolymer dA or dT sequences (e.g., paragraph bridging pages 464-465; paragraph bridging pages 467-468). Example 1.1 of the specification made use of the target sequences AAAAAAGGCG and AAAAAAGGCGAAAAAA, which contain homopolymer A sequences, which one of skill in the art would have recognized as a potential binding site for distamycin A based upon the teachings of Dervan. Lim et al (US Patent No. 7,189,506 B1, cited in a prior action) teaches that distamycin and 21x (a compound comprising netropsin, which is taught by Dervan to bind AT-rich sequences of DNA (e.g., paragraph bridging pages 464-465) each bind an AT-rich DNA sequence and are capable of displacing the binding of NF-κB to its target site, when the target site overlaps the AT-rich sequence bound by distamycin (e.g., column 27, lines 62-67; column 50, line 60 to column 51, line 21; Figures 7-8). Further, Dervan teaches that echinomycin and actinomycin D bind preferentially to GC-rich sequences of DNA (e.g., paragraph bridging pages 464-465), and Examples 1.2-1.3 of the present specification made use of GC-rich target sequences (at least 6/9 bases are G or C). Furthermore, Welch et al (The Journal of Biological Chemistry, Vol. 269, No. 49, pages 31051-31058, December 1994) teach that the binding of antibiotics to DNA can inhibit the binding of zinc finger transcription factors to their target DNA site, and specific transcription factor/antibiotic combinations must be empirically determined (see the entire reference, especially the discussion).

Given the teachings of the prior art with regard to distamycin, actinomycin D and echinomycin binding DNA, and the lack of evidence on the record that any of these compounds or other ligands are capable of binding to Cys2-His2 zinc fingers directly, one would have recognized that Applicants were not in possession of complexes and compositions where a ligand must bind to a Cys2-His2 zinc finger.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 34, 50, 52 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Christopherson et al (Proceedings of the National Academy of Sciences USA, Vol. 89, No. 14, pages 6314-6318, July 1992, cited in a prior action; see the entire reference) in view of Choo et al (WO 98/53059, cited in a prior action; see the entire reference). This rejection was made in

the Office action mailed 11/9/2010 and has been rewritten to address the amendments to the claims in the reply filed 6/15/2011.

Claim 34 is drawn to a complex comprising (a) an engineered, non-naturally occurring Cys2-His2 zinc finger protein, the zinc finger binding domain capable of binding to a DNA target site; and (b) a ligand that binds to the zinc finger protein, wherein the ligand does not comprise the DNA target site, and wherein binding of the zinc finger protein to the target site is modulated when the zinc finger protein is bound by the ligand. The claim indicates that the "zinc finger binding domain" is "capable of binding to a DNA target site." The claim goes on to indicate that "binding of the zinc finger protein to the target site is modulated when the zinc finger protein is bound by the ligand." The specification defines the terms "peptide", "polypeptide" and "protein" as "a polymer in which the monomers are amino acids and are joined together through peptide or disulfide bonds." See page 11, lines 14-16. The specification teaches that the polypeptide will at least have binding capability (e.g., the zinc finger DNA binding domain) and also may have another biological function of a protein or domain (e.g., page 12, lines 7-16; page 67, line 26 to page 69, line 5). Thus, the broadest reasonable interpretation of the term "zinc finger protein" encompasses a protein comprising a zinc finger domain with other domains present in the "zinc finger protein." Furthermore, the specification defines the term "domain" to mean "a linear sequence of amino acids which exhibits biological function." See page 12, lines 7-8. However, the specification indicates, "The term 'domain' also may refer to polypeptides and peptides having biological function. A polypeptide useful in the invention will at least have a binding capability...and also may have another biological function that is a biological function of a protein or domain from which the peptide sequence is derived." See

page 12, lines 12-16. Thus, the broadest reasonable interpretation of the claim includes a complex comprising a zinc finger protein comprising an engineered, non-naturally occurring Cys2-His2 zinc finger and a ligand-binding domain, and a ligand bound to the ligand-binding domain of the zinc finger protein. Claim 50 requires ligand binding to promote binding of the zinc finger to the DNA target site.

Claim 52 is drawn to a composition comprising (i) an engineered, non-naturally occurring Cys2-His2 zinc finger protein, that binds to a target site in DNA; and (ii) a ligand, wherein the ligand does not comprise the DNA target site and further wherein binding of the zinc finger binding domain to the target site is modulated when the ligand is bound to the zinc finger protein. In light of the teachings of the specification, the broadest reasonable interpretation of the claim is a composition comprising a zinc finger protein comprising an engineered, non-naturally occurring Cys2-His2 zinc finger and a ligand-binding domain, and a ligand that binds to the ligand-binding domain of the zinc finger protein. Claim 50 requires ligand binding to promote binding of the zinc finger to the DNA target site.

Christopherson et al teach a complex comprising a polypeptide comprising (i) a DNA binding domain and an ecdysone receptor ligand binding domain; and (ii) a ligand, such as muristerone A, that binds to the ligand binding domain (e.g., pages 6314-6315, Materials and Methods; pages 6315-6317, Results; Figure 2). Christopherson et al teach the polypeptide where the DNA binding domain is selected from a wild type ecdysone receptor DNA binding domain, a glucocorticoid receptor DNA binding domain, an engineered, non-naturally occurring rat glucocorticoid receptor DNA binding domain containing a two-amino acid substitution (G458E, S459G) that alters the DNA-binding specificity; and an *E. coli* LexA DNA binding domain (e.g.,

Figure 2). Christopherson et al teach that each of the DNA-binding and transactivation activities of these proteins were rendered ecdysteroid-dependent when fused to the ligand-binding domain of the ecdysone receptor (e.g., Abstract; pages 6315-6317, Results; Tables 1-2). Christopherson et al teach that novel target-gene specificity was obtained by using the chimeric receptors containing the ecdysone receptor ligand-binding domain fused to heterologous DNA binding domains (e.g., page 6314, paragraph bridging columns; paragraph bridging pages 6317-6318). Further, the transcriptional regulatory activities of the fusion polypeptides are dependent upon the addition of exogenous ligand, allowing one to "switch on" the activator with ecdysteroids (e.g., paragraph bridging pages 6317-6318; page 6318, left column, 2nd full paragraph). Christopherson et al teach that the development of a system for regulated expression of endogenous and exogenous genes in eukaryotic cells should provide an important method to study the function of those gene products (e.g., page 6318, left column, 2nd full paragraph).

Christopherson et al do not teach the complex where the engineered, non-naturally occurring DNA binding domain is an engineered, non-naturally occurring Cys2-His2 zinc finger DNA binding domain.

Choo et al teach that protein-nucleic acid recognition is a commonplace phenomenon which is central to a large number of biomolecular control mechanisms which regulate the function of eukaryotic and prokaryotic cells, such as the regulation of gene expression (e.g., page 1, lines 7-11). Choo et al teach a code which permits the selection of any nucleic acid sequence as the target sequence for the design of a specific zinc finger nucleic acid-binding protein which will bind thereto (e.g., paragraph bridging pages 2-3). Choo et al teach that the zinc finger nucleic acid-binding protein is a protein of the Cys2-His2 zinc finger class capable of binding to

a nucleic acid base triplet in a target nucleic acid sequence, wherein binding to the nucleic acid base triplet by an alpha-helical zinc finger nucleic acid protein is determined according to the disclosed code (e.g., page 3, line 6-27; page 6, line 21 to page 7, line 12). Thus, Choo et al teach a polypeptide comprising an engineered, non-naturally occurring Cys2-His2 zinc finger binding domain, the zinc finger binding domain capable of binding to a DNA target site. Further, Choo et al teach that the disclosed zinc finger binding motifs can be combined into nucleic acid binding proteins having a multiplicity of fingers, commonly at least three zinc fingers (e.g., page 13, lines 6-22). Choo et al teach that the invention provides nucleic acid binding proteins which can be engineered with exquisite specificity, lending to the design of any zinc finger-comprising molecule of which specific nucleic acid binding is required (e.g., page 25).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to replace the engineered, non-naturally occurring DNA binding domain of Christopherson et al with an engineered, non-naturally occurring Cys2-His2 zinc finger binding domain taught by Choo et al because Christopherson et al teach it is within the ordinary skill in the replace the wild type ecdysone receptor DNA binding domain with a heterologous domain, including one mutated to provide altered DNA-biding specificity, and Choo et al teach engineered, non-naturally occurring Cys2-His2 zinc finger binding domains designed by the disclosed rules to bind to any particular target sequence.

One would have been motivated to make such a modification in order to receive the expected benefit of providing polypeptides whose DNA-binding and transactivation activity are regulated by an exogenous ligand as taught by Christopherson for the regulation of any gene targeted by the engineered, non-naturally occurring Cys2-His2 zinc finger DNA binding domain

of Choo et al. By altering the DNA binding specificity one would provide a system for regulated expression of endogenous and exogenous genes in eukaryotic cells to provide an important method to study the function of those gene products. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 34 and 50-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evans et al (US Patent No. 6,333,318 B1; see the entire reference) in view of Choo et al (WO 98/53059, cited in a prior action; see the entire reference). This rejection was made in the Office action mailed 4/19/2011 and has been rewritten to address the amendments to the claims in the reply filed 6/15/2011.

Claim 34 is drawn to a complex comprising (a) an engineered, non-naturally occurring Cys2-His2 zinc finger protein, the zinc finger binding domain capable of binding to a DNA target site; and (b) a ligand that binds to the zinc finger protein, wherein the ligand does not comprise the DNA target site, and wherein binding of the zinc finger protein to the target site is modulated when the zinc finger protein is bound by the ligand. The claim indicates that the "zinc finger binding domain" is "capable of binding to a DNA target site." The claim goes on to indicate that "binding of the zinc finger protein to the target site is modulated when the zinc finger protein is bound by the ligand." The specification defines the terms "peptide", "polypeptide" and "protein" as "a polymer in which the monomers are amino acids and are joined together through peptide or disulfide bonds." See page 11, lines 14-16. The specification

teaches that the polypeptide will at least have binding capability (e.g., the zinc finger DNA binding domain) and also may have another biological function of a protein or domain (e.g., page 12, lines 7-16; page 67, line 26 to page 69, line 5). Thus, the broadest reasonable interpretation of the term "zinc finger protein" encompasses a protein comprising a zinc finger domain with other domains present in the "zinc finger protein." Furthermore, the specification defines the term "domain" to mean "a linear sequence of amino acids which exhibits biological function." See page 12, lines 7-8. However, the specification indicates, "The term 'domain' also may refer to polypeptides and peptides having biological function. A polypeptide useful in the invention will at least have a binding capability...and also may have another biological function that is a biological function of a protein or domain from which the peptide sequence is derived." See page 12, lines 12-16. Thus, the broadest reasonable interpretation of the claim includes a complex comprising a zinc finger protein comprising an engineered, non-naturally occurring Cys2-His2 zinc finger and a ligand-binding domain, and a ligand bound to the ligand-binding domain of the zinc finger protein. Claim 50 requires ligand binding to promote binding of the zinc finger to the DNA target site. Claim 51 requires ligand binding to result in dissociation of the zinc finger from the DNA target site.

Claim 52 is drawn to a composition comprising (i) an engineered, non-naturally occurring Cys2-His2 zinc finger protein, that binds to a target site in DNA; and (ii) a ligand, wherein the ligand does not comprise the DNA target site and further wherein binding of the zinc finger binding domain to the target site is modulated when the ligand is bound to the zinc finger protein. In light of the teachings of the specification, the broadest reasonable interpretation of the claim is a composition comprising a zinc finger protein comprising an engineered, non-

naturally occurring Cys2-His2 zinc finger and a ligand-binding domain, and a ligand that binds to the ligand-binding domain of the zinc finger protein. Claim 53 requires ligand binding to promote binding of the zinc finger to the DNA target site. Claim 54 requires ligand binding to result in dissociation of the zinc finger from the DNA target site.

Evans et al teach products for modulating the expression of exogenous genes in mammalian systems (e.g., column 1, lines 10-12). Evans et al teach a polypeptide comprising (i) a ligand binding domain capable of binding an ecdysteroid; (ii) a zinc finger DNA-binding domain that binds to a response element; and (iii) an activation domain (e.g., column 7, lines 53-62; column 8, lines 24-34 and line 62; column 9, lines 8-12; paragraph bridging columns 17-18). Further, Evans et al teach a ligand that binds to the polypeptide, where the ligand is a compound, such as an ecdysteroid and where ligand binding to the polypeptide modulates binding of the DNA-binding domain to its target response element sequence (e.g., column 5, line 31 to column 6, line 17; column 12, line 23 to column 15, line 4). Evans et al teach that binding of ecdysone (as well as analogs and mimics thereof) induces binding of the polypeptide to the response element to activate gene expression, and binding of an ecdystone antagonist inhibits binding of the polypeptide to the response element to turn off gene expression (e.g., column 5, line 31 to column 6, line 17; paragraph bridging columns 14-15). Evans et al contemplate the modification of existing DNA-binding domains to allow them to recognize new and/or specific target recognition sequences, the use of *in vitro* evolution methods to improve existing DNA-binding domains, and the use of DNA-binding domains which are engineered with novel DNA-recognition specificity (e.g., column 10, lines 14-16; paragraph bridging columns 10-11). Evans et al teach that the products provide the ability to manage the expression of genes introduced into

mammalian cells and animals, which further advances many areas of biology and medicine (e.g., column 2, lines 23-25).

Evans et al do not specifically teach that the engineered, mutated (non-naturally occurring) DNA-binding domains are Cys2-His2 zinc finger binding domains.

Choo et al teach that protein-nucleic acid recognition is a commonplace phenomenon which is central to a large number of biomolecular control mechanisms which regulate the function of eukaryotic and prokaryotic cells, such as the regulation of gene expression (e.g., page 1, lines 7-11). Choo et al teach a code which permits the selection of any nucleic acid sequence as the target sequence for the design of a specific zinc finger nucleic acid-binding protein which will bind thereto (e.g., paragraph bridging pages 2-3). Choo et al teach that the zinc finger nucleic acid-binding protein is a protein of the Cys2-His2 zinc finger class capable of binding to a nucleic acid base triplet in a target nucleic acid sequence, wherein binding to the 5' base of the nucleic acid base triplet by an alpha-helical zinc finger nucleic acid protein is determined according to the disclosed code (e.g., page 3, line 6-27; page 6, line 21 to page 7, line 12). Thus, Choo et al teach a polypeptide comprising an engineered, non-naturally occurring Cys2-His2 zinc finger binding domain, the zinc finger binding domain capable of binding to a DNA target site. Further, Choo et al teach that the disclosed zinc finger binding motifs can be combined into nucleic acid binding proteins having a multiplicity of fingers, commonly at least three zinc fingers (e.g., page 13, lines 6-22). Choo et al teach that the invention provides nucleic acid binding proteins which can be engineered with exquisite specificity, lending to the design of any zinc finger-comprising molecule of which specific nucleic acid binding is required (e.g., page 25).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the polypeptide of the products of Evans et al to specifically include the engineered, non-naturally occurring Cys2-His2 zinc finger binding domains taught by Choo et al as the non-naturally occurring binding domain or zinc finger binding domain of the transcriptional regulatory polypeptide because Evans et al teach it is within the ordinary skill in the art to use zinc finger binding domains and to engineered, non-naturally occurring DNA binding domains to create new binding specificities, and Choo et al teach that it is the Cys2-His2 zinc finger class that is capable of being engineered to bind a particular sequence according to the disclosed code.

One would have been motivated to make such a modification in order to receive the expected benefit of providing a transcriptional regulatory polypeptide capable of binding a particular target sequence with specificity as taught by Choo et al in order to broaden the applications of the products taught by Evans et al for the study of additional genes. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments - 35 USC § 103

With respect to the rejection of claims 34, 50, 52 and 53 under 35 U.S.C. 103(a) as being unpatentable over Christopherson et al in view of Choo et al, and the rejection of claims 34 and 50-54 under 35 U.S.C. 103(a) as being unpatentable over Evans et al in view of Choo et al, Applicant's arguments filed 6/15/2011 have been fully considered but they are not persuasive.

The response asserts that the amendments to the claims make it clear that the ligand binds to the zinc finger protein itself rather than a ligand binding domain. The response asserts that Christopherson, Lim and Evans all relate only to fusion proteins made up of separate heterologous DNA and ligand-binding domains. Thus, the response asserts that the art cannot be combined to arrive at the claimed subject matter.

This argument is not found persuasive. The specification defines the terms “peptide”, “polypeptide” and “protein” as "a polymer in which the monomers are amino acids and are joined together through peptide or disulfide bonds." See page 11, lines 14-16. The specification teaches that the polypeptide will at least have binding capability (e.g., the zinc finger DNA binding domain) and also may have another biological function of a protein or domain (e.g., page 12, lines 7-16; page 67, line 26 to page 69, line 5). Thus, the broadest reasonable interpretation of the term “zinc finger protein” encompasses a protein comprising a zinc finger domain with other domains present in the “zinc finger protein.” Furthermore, the specification defines the term “domain” to mean “a linear sequence of amino acids which exhibits biological function.” See page 12, lines 7-8. However, the specification indicates, "The term 'domain' also may refer to polypeptides and peptides having biological function. A polypeptide useful in the invention will at least have a binding capability...and also may have another biological function that is a biological function of a protein or domain from which the peptide sequence is derived.” See page 12, lines 12-16. Thus, the broadest reasonable interpretation of the claims includes a complex comprising a zinc finger protein comprising an engineered, non-naturally occurring Cys2-His2 zinc finger and a ligand-binding domain, and a ligand bound to the ligand-binding domain of the zinc finger protein.

For these reasons, and the reasons made of record in the previous office actions, the rejections are maintained.

The rejection of claims 52 and 54 under 35 U.S.C. 103(a) as being unpatentable over Lim et al (US Patent No. 7,189,506 B1, cited in a prior action; see the entire reference) in view of Choo et al (WO 98/53059) has been withdrawn in view of Applicant's amendment to the claims in the reply filed 6/15/2011. The claims now require the ligand to bind the zinc finger protein, which is not taught by the references.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is (571)272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Jennifer Dunston/
Primary Examiner
Art Unit 1636